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LOW TITER GROUP O WHOLE BLOOD IN EMERGENCY SITUATIONS

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ABSTRACT In past and ongoing military conflicts, the use of whole blood (WB) as a resuscitative product to treat trauma-induced shock and coagulopathy has been widely accepted as an alternative when availability of a balanced component-based transfusion strategy is restricted or lacking. In previous military conflicts, ABO group O blood from donors with low titers of anti-A/B blood group antibodies was favored. Now, several policies demand the exclusive use of ABO group specific WB. In this short review, we argue that the overall risks, dangers, and consequences of "the ABO group specific approach," in emergencies, make the use of universal group O WB from donors with low titers of anti-A/B safer. Generally, risks with ABO group specific transfusions are associated with *in vivo* destruction of the red blood cells transfused. The risk with group O WB is from the plasma transfused to ABO-incompatible patients. In the civilian setting, the risk of clinical hemolytic transfusion reactions (HTRs) due to ABO group specific red blood cell transfusions is relatively low (approximately 1:80,000), but the consequences are frequently severe. Civilian risk of HTRs due to plasma incompatible transfusions, using titered donors, is approximately 1:120,000 but usually of mild to moderate severity. Emergency settings are often chaotic and resource limited, factors well known to increase the potential for human errors. Using ABO group specific WB in emergencies may delay treatment because of needed ABO typing, increase the risk of clinical HTRs, and increase the severity of these reactions as well as increase the danger of underresuscitation due to lack of some ABO groups. When the clinical decision has been made to transfuse WB in patients with life-threatening hemorrhagic shock, we recommend the use of group O WB from donors with low anti-A/B titers when logistical constraints preclude the rapid availability of ABO group specific WB and reliable group matching between donor and recipient is not feasible.

KEYWORDS Whole blood, ABO- titers, universal blood, blood transfusion, damage control resuscitation

INTRODUCTION

The current use of whole blood (WB) in combat casualty care is primarily motivated by the need for a resuscitative solution that treats both shock and coagulopathy for patients with life-threatening hemorrhagic shock. Whole blood often represents the only available platelet source and may even be the only source of red blood cells (RBCs) and plasma in numerous military operational environments (1). Its use in austere environments for remote damage control resuscitation (DCR) is driven by necessity to improve survival. This is reflected in the doctrinal support for WB use by many North Atlantic Treaty Organization countries as an important source of a balanced transfusion product when blood components are unavailable or limited in numbers (2, 3).

Military medical experience in the recent conflicts in Iraq and Afghanistan has changed transfusion therapy for massive hemorrhage. The DCR principle has gained worldwide acceptance, and trauma patients with life-threatening hemorrhage often undergo transfusion with *de facto* WB, albeit reconstructed from components in a 1:1:1 ratio of plasma to RBCs to platelets (4). The logical question is accordingly: Why not use WB for hemorrhagic shock and thereby substantially reduce recipient exposure to donors, minimize RBC and platelet storage lesion effects, and reduce dilution by additive solutions and anticoagulants (5–8)? A randomized controlled pilot trial sponsored by the US Department of Defense comparing components to modified WB plus apheresis platelet indicated transfusion volumes, and other outcomes were similar in both treatment groups (9).

Because WB can be stored for at least 2 weeks with acceptable levels of coagulation components, WB stored for short periods is a good option to treat trauma victims to handle both shock and hemorrhage while minimizing donor exposure (10).

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The lethal potential of an incompatible transfusion is determined by the number of RBCs hemolyzed. Transfusion of one ABO-incompatible RBC unit is more dangerous than the transfusion of one ABO-incompatible plasma unit because the entire unit of RBCs infused may lyze (and result in a rapidly fatal outcome), whereas incompatible antibodies in plasma are diluted and absorbed in the recipient and are thus not as likely to lyze as many recipient RBCs.

The main immediate risk related to transfusion is the acute hemolytic transfusion reaction (HTR). These reactions are with few exceptions because of major ABO incompatibility. Major ABO incompatibility occurs when ABO-incompatible donor RBCs are infused into a patient with preexisting anti-A and/or -B antibodies. This often-fatal complication is avoided by exclusively transfusing group O RBCs. In emergency settings, both prehospital and in-hospital, there is a general acceptance that using noncrossmatched group O RBCs for immediate transfusion is the safest approach, because the most common cause of lethal HTR is accidental transfusion of incompatible RBCs (11). Pretransfusion testing takes too much time, and rapid testing systems are not generally available, and all blood sampling procedures are dependent on careful patient identification and sample handling, which can be difficult to maintain in emergency or austere situations. The transfusion of ABO identical WB assumes the risk of a severe HTR due to human error.

Minor ABO incompatibility is defined as transfusion of donor anti-A and/or anti-B to a patient whose RBCs carry A or B antigens. Clinical consequences are typically minor and frequently subclinical (12). Platelet transfusions with ABO-incompatible plasma occur routinely in hospitals in the United States and Europe because of inventory constraints. There is a low frequency of clinical hemolytic reactions (approximately 1:10,000), and most of these are caused by units from group O donors with high titers of anti-A (13). The transfusion of group O WB theoretically incurs the same nonfatal risk of minor ABO incompatibility as nonidentical platelet transfusion.

It is therefore a paradox that in some countries the regulatory authorities have required WB transfusions to be ABO identical to protect against minor ABO incompatibility, while permitting transfusion of ABO-incompatible platelet units containing comparable volumes of plasma to a corresponding WB unit (3, 14). The argument that platelet shortages force us to accept the use of nonidentical platelet concentrates should also be valid for low-titer group O WB transfusions in emergency settings.

These inconsistent policies are also challenged by the vast experience with low-titer group O WB in previous wars. Ironically, the argument for using group O low-titer WB was to avoid HTRs, and the historic clinical experience infers that this measure was very successful, as reports of fatal HTRs due to minor ABO incompatibility are vanishingly rare (two cases) in combat registries (15).

In this brief review, the risks and benefits of ABO group–specific WB versus low-titer group O WB are discussed. Titer is defined as the reciprocal value of the highest serum dilution causing agglutination. When the clinical decision has been made to transfuse WB in patients with life-threatening hemorrhagic shock, we recommend the use of group O WB from donors with low anti-A/B titers when logistical constraints preclude the rapid availability of ABO group–specific WB, and reliable group matching between donor and recipient is not feasible. A specific protocol on the collection and transfusion of low-titer group O WB in the prehospital setting is described elsewhere in this supplement (1).

Blood ABO groups and Rh(D) group

The ABO blood groups are defined by the structure of carbohydrate chains on the extracellular surface of RBC plasma membranes and are shared with some bacteria and plant seeds (16–19). As antigenic substances are absorbed from the intestinal bacteria, all individuals from 3 months of age develop preformed antibodies of immunoglobulin M (IgM) type, produced from the intestinal immune system, against the missing A or B blood groups in their plasma. These so-called naturally occurring antibodies are complement activating, usually strongly hemolytic, and are the causative agents of most fatal HTRs. The ABO blood group substances also exist as free macromolecules in the plasma and will easily form soluble ABO immune complexes with the corresponding antibodies in the case of the transfusion of incompatible anti-A/-B antibodies. Exposure to vaccines produced from bacteria and viruses has been shown to boost the formation of anti-A and -B antibodies, and antibodies of both IgM and IgG type will be affected (17).

As an RBC concentrate typically contains less than 10 mL of plasma, group O RBCs can be used for transfusion regardless of the ABO blood group of the recipient. In case of WB or apheresis platelets, each unit usually contains about 200 to 300 mL of plasma. A transfusion, depending on the titer of antibodies and amount of plasma, may result in a clinically relevant direct intravascular hemolysis of the RBCs of a non–group O recipient. The amount of antibody is measured by titration, for the IgM type in a saline dilution, and for the IgG type with an anti–human globulin technique. Titration of anti-A and anti-B has long been used to select safe universal group O donors (13, 20, 21). Although titration methods show significant interlaboratory variation, and there are no internationally approved references or acknowledged "safe" low titer levels for anti-A or anti-B, the blood regulatory establishments of several countries have published standards for titering group O blood products (22–26).

Rh incompatibility is of little consequence in emergency resuscitation of most male patients. Rh-negative products can be given preferentially to female patients of child-bearing potential, or Rh-negative females given low volumes of Rh-positive products can, in some cases, be treated with Rh immune globulin to reduce the risk of alloimmunization to Rh antigens and subsequent fetal hemolysis in future Rh-positive pregnancies.

History and current status of ABO compatibility for WB transfusions

Type O WB has been widely used by military forces as "universal blood" for emergency transfusions since World War I, especially in far-forward conditions. In 1942, a systematic evaluation of the clinical effects of group O WB

transfusion to group A recipients was published by Aubert and colleagues (27, 28). They found several publications arguing that the transfusion of ABO-incompatible plasma was dangerous, but none documenting actual case reports with adverse reactions. Their own results were based on 15 cases with group A recipients receiving serum or plasma group O containing high- or low-titer anti-A isoagglutinins. Twelve of the reported cases received high-titer (IgM >256) plasma or serum with IgG titers ranging from 512 to 16,284, and total volumes infused ranged from 30 to 500 mL (average, 327 mL). Of the 12 cases receiving serum or plasma containing high-titer isoagglutinins, five developed a clinical syndrome, the most striking symptoms of which were moderate or severe aching pain across the small of the back, often radiating to the thighs, constricting sensations in the neck and chest, intestinal colic, and nausea. Although these symptoms are suggestive of symptomatic hemolytic reactions, no reactions were observed that caused more than a transient deterioration in the general physiological condition.

During World War II, almost all blood used in the US Army medical service was group O WB regardless of the blood group of the recipient (29). In a group of 265 transfusions with ABO-incompatible group O WB, there were three reactions with hemoglobinemia and hyperbilirubinemia but without other serious clinical symptoms. All the implicated blood units had isoagglutinin (anti-A/anti-B) titer (IgM) that exceeded 500. However, after a report in 1944 of a severe hemolytic reaction from a unit with an antibody titer of 8000, the US Army introduced a policy in which all group O blood units with an ABO antibody titer (IgM) greater than 250 were labeled "high titer" and could be used only for group O patients (30). Group O blood has been extensively used in military scenarios since World War II, and there are very few reports of serious adverse effects (31, 32).

In the Korean War, the only WB shipped to the war zone was group O, and all units were labeled low- or high-titer group O units. The total amount of blood used was almost 400,000 units. Low-titer WB was used for all non–group O recipients (33). No reactions, in fact, were reported in Korea that might have been ascribed to "group O universal donors". In practice, the division of group O blood into high and low titer, on the basis of a titer of less than 256, thus appeared to be safe (34).

In the Vietnam War, the requirement for WB climbed steadily from less than 100 U per month in 1965 to a peak of 38,000 U per month in February 1969. In early 1965, it was decided that only universal donor low-titer group O should be shipped to Vietnam. As the blood requirements increased, the policy was subsequently changed to utilize fully the available donor population; the first shipment of group A WB arrived in December 1965, and shipments with random blood group distribution arrived in January 1966. The clearing companies and forward surgical hospitals continued to use only group O low-titer WB because they could not perform pretransfusion testing or compatibility testing (35). A total of 230,323 WB units (all ABO groups included) were transfused between September 1967 and February 1969. Only 1 of 24 reported HTRs was caused by ABO-incompatible antibodies in a group O unit, and this reaction was attributed to a high-titer–labeled unit (actual titers: IgM 256 and IgG 32768) used by mistake as universal blood in a far-forward situation (30, 31, 36, 37).

After the Korean War, with the introduction of RBC concentrates and additive solutions, only transfusions with WB or platelet concentrates continued to carry the risk for adverse reactions from transfused ABO-incompatible antibodies. Group O WB (nontitered) continued to be used, albeit uncommonly, as universal blood in austere emergency situations during the wars in Iraq and Afghanistan where ABO typing was not feasible (38). Group-specific WB transfusions in Iraq and Afghanistan in larger combat hospitals with laboratories were more common because of the capability to perform ABO typing and the concern for HTRs (7). In one published evaluation where a significant portion of WB was group O (nontitered) and transfused to non–group O patients, there were no reports of hemolytic complications (38–41).

The acceptance and common use of low-titer group O WB as the preferred safe universal blood came to an almost complete stop in the 1970s as blood centers attempted to maximize component availability by producing RBC concentrates and plasma-containing products. The use of WB has continued in military conflicts nevertheless, including during the recent conflicts in Iraq and Afghanistan. Military transfusion practice differs significantly among North Atlantic Treaty Organization countries ranging from bans on the use of WB to accepting WB. Some policies accept use of group O at forward installations only. The current US military medical doctrine requires use of ABO group–identical WB because of concern regarding HTRs from donors not prescreened to determine anti-A or anti-B titers (42). On the other hand, at US military facilities, transfusions of nontitered group O platelet concentrates containing similar volumes of plasma are accepted universally. Overall, however, US military doctrine intentionally provides flexibility to adapt practice based on mission requirements (43).

UK defense policy advises that where emergency donor panels are used, these would normally consist only of group O volunteers. However, if the operational theater or exercise area contains a state-registered biomedical scientist, then donors with group A or B can also be included. Donors should be identified in advance, and selection must comply with national selection guidelines. Blood testing is undertaken by one of the UK blood transfusion services. Serologic testing includes ABO and Rh D grouping including Rh variants, hemolysins for group O donors and alloantibody screening. Approximately 3% to 10% of all donor samples are categorized as high titer for hemolysins.

Australian military policy is that all donor units must be ABO typed, even in an emergency. It is desirable to perform an antibody screen on the donor serum, but this may be omitted in emergency field conditions. Ideally, ABO-specific blood should be used, but "group O blood can be given if no laboratory facilities are available" (44–46).

The Norwegian Military Medical policy opens for the emergency use of fresh WB in field hospitals. This policy is currently being scrutinized for implementation and permits the use of standard virus-tested, leukoreduced (platelet sparing

filtered), cold-stored WB type O low titer (indirect antiglobulin technique <400, saline technique <100) as a "carried along" alternative when a prescreened walking donor pool is unavailable. In situations where immediate transfusion is crucial for survival and "carried along" WB is unavailable, the use of untitered O WB may be considered, but should never delay transportation to adequate surgery.

French military policy accepts use of group-specific WB for major trauma resuscitation in resource-limited settings, particularly for coagulopathic patients in hemorrhagic shock who require massive transfusion, and especially when platelets are indicated and are otherwise unavailable. It allows the use of group O nontitered WB under exceptional circumstances when immediate transfusion is crucial for survival and ABO-identical donors are not available. Whole blood may be stored at room temperature for up to 6 h and then under refrigeration for up to 24 h after collection. Whole blood should be obtained only from prescreened volunteer donors (47–49).

ABO incompatibility and platelet transfusion risks

In civilian medical service, the problems related to the transfusion of group O WB to non–group O recipients disappeared with the introduction of component therapy (RBC, plasma, and platelet units) and the virtual elimination of WB transfusion in adults. Standard practice for platelet transfusions is to allow incompatible ABO group transfusions if necessary. Adverse effects including hemolytic reactions are more readily observed and reported in civilian systems than in combat settings. In most European countries, all transfusion reactions are reported via a mandatory hemovigilance system and compiled. A total of 25 reports (mostly case reports) of hemolytic reactions in connection with platelet transfusions from 1975 to 2009 have been recently evaluated in detail (18). From 30 patient cases of which 25 were malignancies, mostly leukemia, there were only two fatalities that could be linked to a HTR because of incompatible platelets in otherwise very sick cancer patients. In 1998, Mair and Benson (13) reported one reaction in 46,176 platelet transfusions, of which 21% had minor ABO incompatibility; these data suggested a risk of a moderate HTR in 1:9600 incompatible platelet transfusions. When group O platelet components are titered, this risk is further diminished. In the UK SHOT Haemovigilance report of 2011 and 2012, there was 1 case of HTR by a platelet transfusion from a total of 613,365 (caused by a group O high-titer donor). Assuming about 20% of platelets are administered out of group, the risk of HTRs caused by incompatible plasma can be roughly estimated around 1:120,000. These reported risks for platelet transfusions are pertinent for the assessment of the risk of group O WB because they are similar regarding the risk for plasma incompatibility and rare risk of RBC incompatibility.

As platelets are stored in plasma, the experience at the Mayo Clinic with the use of group A plasma as a universal donor indicates that this may be a safe practice. These data also support the safety of transfusing plasma with minor ABO incompatibility (50).

ABO-incompatible transfusion reactions

The adverse effect from the transfusion of ABO-incompatible plasma can be separated into immediate, delayed (within 1 h to 4 days), and late effects. Of these, only immediate effects contribute significantly to morbidity and mortality in emergency transfusion situations. For immediate adverse reactions, the severity is correlated to the titer of the transfused antibody. To minimize the risks of ABO-incompatible transfusion reactions, all plasma-containing blood component units should be collected from donors with a low titer of ABO antibodies if the intent is to give these units as group O WB. It is also important that each unit should

Table 1. **Clinical decision making matrix comparing risks and benefits of WB transfusion strategies**

	ABO group specific WB	Low-Titer Group O WB
Benefits	1. ABO compatibility of RBCs and plasma after typing of donor and recipient or full crossmatch	1. ABO compatibility of RBCs with all major blood groups
		2. Few minor ABO incompatibility transfusion reactions
		3. No need to ABO group or crossmatch the recipient if immediate transfusion is crucial for survival
		4. Readily available due to high frequency of low-titer group O donors (approximately 95% 70% of group O donors if IgG <400, IgM <100)
		5. Safer in chaotic and remote situations (no risk of mismatched RBC transfusion due to clerical error)
Risk or burden	1. Increased risk of a hemolytic reaction due to major ABO incompatibility*	1. Risk of mild to moderate hemolytic reactions due to minor ABO incompatibility. No WB data available. Data from titrated donors platelet transfusions estimated 1:120,000†
	2. Increased risk of underresuscitation due to limited availability of some ABO group specific donors	2. Risk of severe hemolytic reaction if anti-A/B titer not accurately identified (clerical error)‡
	3. Need to ABO group donor and recipient	3. Need to titer group O donors
		4. Excludes 5% 30% of group O donors§ (depending on critical titer for anti-A/B used)

* In civilian hospital settings: wrong blood 1:15,000; ABO-incompatible 1:40,000; HTR 1:80,000 (52).
†Estimated from UK SHOT 2011 2012 based on estimated 20% out-of-group platelet transfusions (13).
‡No fatal reactions reported from Korea where approximately 400,000 group O labeled (high and low titer) WB units were transfused.
§NHS Blood and Transplant (26).

be tested for antibody titer because donor antibody levels can fluctuate. There is insufficient evidence to justify a policy that a donor with low-titer antibodies will maintain the low-titer status consistently over time. Even though there is no officially set international standard for titers, most authorities seem to accept an anti-A and -B titer less than 100 for IgM and 400 for IgG type antibodies (21, 30–32, 51). These levels also coincide with the UK NHS national standard of hemolysins and would be compatible with the standards in most European countries and the United States (26).

CONCLUSIONS

Based on the published data and clinical experience during decades of conflict, it is our opinion that low-titer group O WB is the preferred alternative for emergency transfusions where safe ABO-identical transfusions cannot be ensured (Table 1). This is especially true for austere environments, including the prehospital setting, where laboratory facilities are unavailable, and precollected and titered group O blood can be delivered, or where blood from prescreened donors can be collected. Remote DCR requires early use of blood products to reduce death from hemorrhagic shock. By eliminating the need for ABO typing and matching blood transfusion can be instituted earlier, the major ABO HTRs that may occur when the wrong group-specific blood is used in this setting can be avoided. Further research, particularly in the automation and standardization of hemolysin titration and the variability of antibody titers in individual donors over time, is required to optimize this lifesaving therapeutic option. If these additional studies can be completed, it may be possible to translate the military and remote DCR experience to civilian medical practice where early resuscitation could be performed safely with less donor exposures than currently occur with 1:1:1 massive transfusion protocols.

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